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### aSERTaining conflict in mice

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## SUMMARY

Violence has proven to be a costly behavior to our economy financially, physically and psychologically. This fact is only further strengthened by a lack of adequate intervention options currently. Effective prevention strategies thus require a better understanding of the underlying bio-behavioral mechanisms that mediate aggressive and violent behavior. Experimental laboratory models of aggression and violence in rodents and other animal species are indispensable to obtain these goals. Similar to humans, rodents compete with each other to secure territory, status, mates, offspring, food and other resources. Although most individuals respond with appropriate and well-controlled forms of aggressive behavior, certain individuals abnormally escalate their aggression and behave violently. Conflict behavior amongst conspecific animals has thus been ambiguous in that it has an adaptive and a maladaptive dimension to it. Adaptive aggression has been studied extensively both in the wild and under laboratory conditions and has been carefully characterized using multiple approaches. In contrast, research on animal violence has long been shrouded owing to several deterrents including the lack of proper definitions and operational criteria to distinguish violence from adaptive aggression, lack of biologically relevant and valid animal models/methodologies as well as ethical objections. The operational definition in particular has been a considerable challenge in that violence is considered either to be quantitatively (escalated form of aggression, characterized by intense and prolonged durations of offense) or qualitatively (unconventional' characterized by lack of ritualistic pre-warning

signals, indiscrete and injurious attacks regardless of the sex, social status, free-moving/anaesthetized state of the opponent) different from adaptive aggression. In this thesis, we have now demonstrated clear ‘qualitative’ differences between violent and adaptive forms of aggression using mice genetically selected for high/low aggressiveness using ethological, pharmacological and molecular approaches. Further, we have now identified adaptive aggression as a means of social communication achieved via a sequence of flexible yet constrained actions amongst conspecifics and violence as a disruptive communication aimed primarily to prevail and induce harm without any concern for the subjugated conspecific. The short attack latency (SAL) mouse line was shown to display relatively poor pre- (ritualistic) and post-escalation behaviors over escalatory behaviors. In addition, we also observed an unchanging agonistic repertoire (invariant inter- and intra- individual variation) in the SAL mice over a period of several successive aggressive interactions with a docile male opponent. We interpreted this constancy as behavioral inflexibility, which was also demonstrated previously in the SAL mice using non-social contexts. At an ethopharmacological level, while the SAL mice were shown to display a fluoxetine-insensitive violent phenotype, the other high aggressive mouse lines were shown to reduce their aggressiveness upon chronic fluoxetine treatment. This observation, prompted us to assess the functionality of two key components regulating 5-HT levels, i.e., the 5-HT biosynthesizing enzyme tryptophan hydroxylase (TPH) and the serotonin reuptake transporter (5-HTT). The latter is also the principal molecular site of pharmacological action of the SSRI, fluoxetine. While no differences in the 5-HT biosynthetic capacity were found between the high-and low-aggressive mouse lines, low 5-HTT functionality was observed specifically in the SAL mice. This constitutively low 5-HTT activity may not only account for the insensitivity to SSRI’s in these animals, but may also be responsible for the low 5-HT levels reported previously in the SAL line upon repeated aggressive experiences. However, despite the low 5-HTT activity, we did not find low brain 5-HT levels in naïve SAL mice. This in turn indicates that (innately) low 5-HT levels are not necessary for initiating high levels of aggressive behavior. Rather, it suggests that aggressive behavior and/or winning experiences may rapidly alter regulatory components (5-HTT for instance) of the 5-HT system that may eventually lower 5-HT levels and consequently increase violence. Finally, the display of context-independent and indiscriminate aggression and behavioral inflexibility combined with neurochemical findings (namely low 5-HT levels after repeated aggressive experiences, low basal heart rates and low glucocorticoid responses reported earlier) makes SAL mice a suitable candidate for investigation of instrumental forms of violence for future.